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West Point PA 19486

January 22, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

RE: [Docket No. 01D-0489] Draft "*Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees*"

Merck & Co., Inc, is a leading worldwide, human health product company. Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds or potential drug candidates at one time through comprehensive, state-of-the-art Research and Development (R & D) programs that include: basic research and discovery, developmental studies in animals, manufacturing quality assurance testing, and human clinical research.

In the course of bringing product candidates through clinical research, Merck designs and conducts hundreds of clinical trials, annually. Each clinical trial conducted is intended to evaluate the safety or efficacy of product candidates for use in a wide range of serious, life-threatening or chronic illnesses or medical conditions. Through this extensive clinical trials experience, Merck physicians and scientific professionals routinely interact with medical professionals who are involved with clinical trials Data Monitoring Committees (DMCs).

For these reasons, we are very interested and well qualified to comment on the Food and Drug Administration's (FDA's) proposed Draft "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees" (hereafter referred to as *The Draft Guidance*).

General Comments

We commend the FDA for providing *The Draft Guidance* as a resource for sponsors to provide to clinical professionals who will conduct or otherwise participate in clinical trials intended for determinations of safety or effectiveness. In general, Merck's comments below address points in *The Draft Guidance* that, if clarified, would prevent confusion or balance the discussions in the document. In addition, our experience indicates that FDA's *Estimated Annual Reporting Burden*, in Table 1, is significantly underestimated. Specific time estimates are provided below.

Overall, FDA allows flexibility of interpretation and use of this document by acknowledging concepts, but not specifying rigid or restrictive limitations in how these concepts must be

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implemented. We commend FDA's foresight in recognizing the dynamic nature of clinical research.

SPECIFIC COMMENTS AND RECOMMENDATIONS
The following comments address specific sections in *The Draft Guidance.*

1. INTRODUCTION AND BACKGROUND
Merck Comment: On page 1 in paragraph 3, *The Draft Guidance* states, "The DMC advises the sponsor regarding the safety of ... participants ... yet to be recruited...." Does this statement imply that a Data Monitoring Committee (or DMC) has a responsibility to the broad population of patients with a disease within a medical community? Or, does it mean that the DMC's responsibility is restricted to patients in a specific clinical trial in which the sponsor is testing a drug candidate? A DMC might interpret this ambiguity in such a way that it would put participants in a specific clinical trial at risk, in order to achieve results so convincing that the medical community *at large* would be more likely to make use of the trial data in the future.

Merck Recommendation: The document should state that it is not appropriate to put clinical trial participants at unusual risk in order to achieve a result that would benefit future patients.

2. DETERMINING NEED FOR A DMC
Merck Comment: In the introduction to this section of *The Draft Guidance*, and, again, under 2.2 *Practicality of DMC Review*, FDA acknowledges that there are many factors that must be considered in determining the need for a DMC in any clinical setting. Although FDA does not mention the need or appropriateness of a DMC in post-marketing settings, e.g., in large trials within an approved indication, it does acknowledge that there are situations where there may be no need to establish a DMC for the purposes of general safety monitoring. Another exception might be as noted in *2.2 Practicality of DMC Review,* if "...the trial is likely to be completed quickly, a DMC might not have an adequate opportunity to contribute."

Merck Recommendation: We commend FDA for taking this reasonable approach and encourage FDA to continue to recommend that a DMC might be considered to ensure scientific validity, but that there are cases when a DMC may not be necessary.

4. DMC ESTABLISHMENT AND OPERATION
Merck Comment **4.1 Committee Composition:** On page 6, FDA notes, "...the ability of DMCs to provide the anticipated ...assurance of patient safety and trial integrity depends on appropriate selection of DMC members." FDA goes on to endorse several types of technical expertise which make an individual particularly valuable to a DMC, namely, medical training, statistical knowledge, specialized scientific training (e.g., toxicology, epidemiology, bioethics, etc.) and administrative ability. Several other abilities are noted and given equal standing, such as gender, ethnic background, geographic origin and conflict-free political associations, e.g., patient advocates.

DMC participants who are not capable of understanding important clinical trials research concepts or applying basic ethics into decision-making and group deliberations will undermine the DMC's ability to operate efficiently and effectively. That DMC runs the risk

that unqualified individuals may misinterpret clinical trial data and may be more inclined to terminate studies for reasons such as early promising or adverse results, which often are not sustained as the study proceeds further.

Merck recommendation 4.1: FDA should emphasize in *The Draft Guidance* that experience and expertise should be the primary criteria for membership on a DMC.

Merck Comment **4.2 Confidentiality of Interim Data and Analyses:** On page 7, *The Draft Guidance* does not distinguish between interim analyses prepared for the purposes of a report to the DMC and interim analyses pre-specified in the protocol for purposes of publication and/or filing an application for marketing approval. The parties involved in limited unblinding may differ substantially in these two scenarios.

In the latter case, although uncommon, the sponsor and/or steering committee may be unblinded to grouped results, though not to individual treatment allocation. This scenario would likely require FDA concurrence in advance (see page 22, **6.6 Use of Interim Data in Regulatory Submissions**) and may have more significant implications for adjustment of the Type I error.

Merck Recommendation 4.2: *The Draft Guidance* should distinguish between interim analyses prepared for the purposes of a report to the DMC and interim analyses that may have been pre-specified in the clinical protocol for purposes of publication and/or filing of a marketing application.

Merck Comments *4.3.1.4 Format of Interim Reports to the DMC and Use of Treatment Codes:*
(1) On page 9 in paragraph 1, *The Draft Guidance* states, "The statistician preparing the reports to the DMC should ***ideally*** be independent of the sponsor." [Emphasis added] As a sponsor of many clinical trials, Merck disagrees with this approach from a practical, operational perspective. While one cannot argue with the need for the sponsor to remain blinded throughout the trial, contracting an independent statistician to prepare the DMC reports necessarily requires the sponsor to lose some quality control over the analyses of data. Since the sponsor has the most to lose from inadvertent unblinding or from incorrect or inappropriate analyses, contracting these functions to outside consultants can be problematic.

An alternative is to unblind a statistician within the sponsor's organization. Preferably, this unblinded internal statistician is one who will not be directly involved with the study details or decisions regarding the conduct or analysis of the trial, and will be separate from the operation of this trial. This statistician will prepare reports with the clear understanding throughout the organization that the unblinded results will remain known only to this individual and to the DMC.

The internal statistician is likely to have more experience with the sponsor's trial operations and more incentive to control his/her actions, than a consultant is. Although there might remain a lingering suspicion that unblinded results or signals may be leaked inadvertently by the unblinded internal statistician, there is no guarantee that an external statistician would be any more successful in safeguarding confidentiality of results. Indeed, an external

statistician, perhaps unfamiliar with the science behind the compound, the study population and disease and related clinical literature, may cause other operational mishaps in this complicated process.

(2) On page 10 in paragraph 1 (last line), the choice of terms does not follow the logic of this paragraph and it appears that "Additionally" should, in fact, be "For example."

Merck Recommendations re: *4.3.1.4*:
(1) *The Draft Guidance* should acknowledge, through a more balanced discussion of the *pros* and *cons*, that an unblinded statistician within the sponsor's organization might be an acceptable arrangement under appropriate circumstances. It would not be unreasonable to expect the unblinded statistician to sign a formal confidentiality statement. This approach should be acknowledged in section *6.4 Conduct of the Interim Analysis*, as well.

(2) Change "Additionally" to "For example," in the last sentence.

Merck Comments *4.3.2. Statistical Methods*
(1) On page 10 in paragraph 1, *The Draft Guidance* supports stopping for futility. On Page 11, *The Draft Guidance* mentions protection of Type I error "even when there is a stated intention to stop early only for futility reasons...." In principle, this may work, but it is not clear in *The Draft Guidance* when and how this may be done in practice.

(2) A detailed data analysis plan (DAP) is typically finalized before complete unblinding of the database occurs, not before the initiation of interim monitoring by a DMC. Therefore, requiring completion of the DAP at an earlier stage could present some logistical difficulties. The standard operating procedures (SOPs) of the DMC are completed in advance of the interim monitoring; they are required to be submitted to FDA at the same time the protocol (which also includes a *data analysis* section) is submitted. Therefore, submission of the DAP any sooner than just before full unblinding at the completion of the study should not be necessary, as implied on page 10 of this section.

Merck Recommendations re: *4.3.2:*
(1) It would be helpful for FDA to provide additional guidance regarding when and how it is appropriate to stop a trial for futility.

(2) A DAP should not be required to be submitted any time prior to unblinding, since it is very likely to be amended, and should be, if new hypotheses that the trial can address are generated while the trial is running.

4.4 **Potential DMC Responsibilities**
Merck Comment 4.4.1. Interim Monitoring: The public interest is best served when a DMC recommends early termination or modification of a clinical trial only if there is overwhelming evidence for benefit or strong evidence for harm. Although some guidance on the asymmetric stopping rules might be useful, at a minimum FDA should emphasize that a DMC should not recommend stopping a trial unless harm has been established beyond a reasonable doubt. In 4.4.1.1 *Monitoring for Effectiveness*, FDA has wisely chosen to advise early termination only "when the data are truly compelling."

Merck Recommendation 4.4.1: We concur with FDA's clear recommendation that stopping a trial should based on the best available evidence.

Merck Comment 4.4.1.2: *Monitoring for Safety*: FDA may want to include in *The Draft Guidance* mention of other ways to evaluate whether or not to stop a trial for safety (in 4.4.1.2 *Monitoring for Safety*). For example, Bayesian analysis/update could be mentioned as a plausible approach, since it is generally recognized as a useful tool for purposes of monitoring safety. Bayesian analysis can provide the DMC with a visual progression or measurement of its safety concerns through posterior densities, among other things. Also, multiple looks are intrinsically handled by the Bayesian analysis principles (e.g., refer to Don Berry's articles in 1985 SIM & 1987 *American Statistician* on Bayesian interim analysis in clinical trials). There is also the important issue of adjustments for multiplicity in evaluating multiple safety findings, in order to avoid inappropriate conclusions to stop a trial.

Merck Recommendation: FDA should consider addressing the issue of acceptability of Bayesian methods for monitoring safety, in *The Draft Guidance*.

Merck Comment 4.4.1.3. *Monitoring Study Conduct*
In **2.3 Assurance of Scientific Validity** on page 4, *The Draft Guidance* is very clear in its advice that all recommendations concerning inclusion criteria, endpoints, etc., should be made by a blinded sponsor. However, in *4.4.1.3. Monitoring Study Conduct,* this issue is less clear and could be construed as in conflict. One might interpret *4.4.1.3* as proposing that the DMC make recommendations concerning these kinds of issues. Similarly, in *4.4.1.4 Consideration of External Data,* FDA suggests that the DMC should make recommendations based on data external to the trial.

Merck Recommendation *4.4.1.3:* The DMC should consider all information, including information external to the trial when reviewing the interim data and making recommendations concerning patient safety. However, *The Draft Guidance* should clearly state that the DMC should not make recommendations regarding study conduct that could more appropriately be made by the blinded sponsor, without consultation with the sponsor.

6. INDEPENDENCE OF THE DMC

Merck Comment 6.4. **Conduct of the Interim Analysis:**
On page 20, FDA makes a valid comment on the risk to the integrity of the trial when a sponsor's statistician is unblinded. Nevertheless, the remainder of the discussion of this issues is not similarly balanced, when it concludes, "the integrity of the trial is *best protected* when the statistician preparing unblinded data for the DMC is external to the sponsor ..." [Emphasis added]

The Draft Guidance states that "sponsors often wish to maintain control of the data ...", but implies that there's no valid reason to do so. As noted above, the sponsor assures the integrity and quality of the trial in order to prevent inadvertent release of sensitive information. Consequently, a sponsor's need to maintain operational and quality control should not be minimized. Indeed, the sponsor's statistician is often more committed to the trial, and more knowledgeable about the protocol and data management issues, than an

independent statistician would be. Therefore, it is not clear that an independent statistician would best protect the integrity of the trial.

Merck Recommendation 6.4: As noted in *4.3.1.4 Format of Interim Reports to the DMC and Use of Treatment Codes* (above), fair balance in presentation of the *pros* and *cons* of contracting independent statisticians should be maintained or data supporting the conclusion that one is superior to the other should be provided in *The Draft Guidance*.

Table 1. -- ESTIMATED ANNUAL REPORTING BURDEN
Merck Comment: This summary underestimates the "Hours per Response" required to prepare:
(1) the Standard Operating Procedures (for the DMC)-- 4 hours / response; and,
(2) the Data Analysis Plan (or statistical approach) -- 8 hours / response.

In Merck's experience, a minimum of 12 hours more appropriately reflects the time required to accomplish each of these activities, when one considers all the reviews and revisions necessary.

Merck Recommendation: The data in Table 1. -- ESTIMATED ANNUAL REPORTING BURDEN should be revised as follows:
(1) the Standard Operating Procedures (for the DMC)-- 12 hours / response; and,
(2) the Data Analysis Plan (or statistical approach) -- 12 hours / response.

Summary
In summary, *The Draft Guidance* will be an excellent resource for sponsors to use in establishing and operating Clinical Trial Data Monitoring Committees, after certain clarifications are made.

We welcome the opportunity to comment on *The Draft "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees"* and, if appropriate, we would be pleased to meet with you to discuss these issues.

Sincerely,

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